IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Patent Application of:

Christopher J. D. POMFRETT, *et al.* Atty. Ref.: LSN-39-314

Serial No.: 10/553,745 Art Unit: 3736 – Conf. No.: 6133

Filed: October 18, 2005 Examiner: Michael C. Stout

For: NERVOUS SYSTEM MONITORING METHOD

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. §1.132

I, Dr. Christopher John Douglas Pomfrett, do hereby declare and state as follows:

1. I am a clinical scientist and a lecturer in Neurophysiology applied to anesthesia at the University of Manchester in the United Kingdom. I obtained a BSc degree in Comparative Physiology with Zoology from Queen Mary College, London University, with first-class honors in 1983. I went on to undertake post-graduate research in the field of neurophysiology at The Medical College of St. Bartholomew's Hospital, London, where I was awarded the degree of doctor of philosophy. I have twenty-two years of post-doctoral experience in physiological measurement, including experience of electroencephalography (EEG), electrocardiology (ECG) and other devices used to measure patients in the operating room. I am also experienced in intracellular and extracellular neurophysiology.

2. I am a co-inventor of the inventions claimed in U.S. patent application Serial No. 10/553,745 ("the Application"). I am, therefore, fully familiar with the

Application. I have read the office action issued by the U.S. Patent and Trademark Office on June 1, 2009, and have considered the Boone, Trivedi and John documents cited therein.

3. I wish to point out that there is a very significant and fundamental difference between the disclosures of Trivedi and John on the one hand, and Boone on the other hand. I first discuss the disclosures of Trivedi and John, and then the disclosure of Boone below.

Trivedi and John: EEG Measurement

4. Both Trivedi and John relate to methods for electroencephalogram (EEG) measurement of brain activity. This is a well known technique for monitoring neural activity. The technique is described in a seminal text in this area, *Principles of Neural Science* by Kandel, Schwarz and Jessel, McGraw-Hill Companies, Inc. (2000). An extract from this text discussing the use of EEG measurement forms Exhibit A to this Declaration. I wish to particularly refer to pages 914-915 which explain the nature of EEG measurement, and also to page 916, left-hand column, first full paragraph. The extract on page 916 makes two important points:

(i) "EEG is an attenuated measure of the extracellular current flow from the summated activity of many neurons." That is, EEG is an entirely passive measurement methodology which is concerned with monitoring current which naturally flows within neurons of the brain. That is, no current or voltage is applied to a subject during EEG measurement. On the contrary, electrodes are used to measure current which flows within and around the neurons as a result of physiological activity.

(ii) "The surface EEG predominantly reflects the activity of cortical neurons close to the EEG electrode. Thus deep structures such as hippocampus, thalamus or brain stem do not contribute directly to the surface EEG." The inherent nature of EEG measurement means that it can measure only activity towards the surface of

the brain. As such, it is incapable of monitoring activity of deep structures which are located relatively far from the surface of a subject's head.

5. It is clear to me that the disclosures of Trivedi and John are entirely concerned with EEG-based systems.

Boone: EIT Measurement

6. The Boone citation relates entirely to tomographic measurement. Here, a current is applied between a pair of electrodes, and potential differences resulting from application of the current are measured by other electrodes. This allows calculations of impedance to be carried out. The measurements of Boone are, therefore, not entirely passive. Instead, Boone measures the effect (in terms of potential difference) which is caused by application of a particular current (see col. 4, lines 7-32). As such, the measurements made by Boone are fundamentally different from those made in an EEG system relating, as they do, to potential differences created by application of particular currents, not to currents which are created by physiological activity.

Fundamental Differences between EIT Measurement and EEG Measurement

7. The fundamentally different nature of EIT measurement and EEG measurement is such that techniques applied in the context of one measurement methodology would not be considered by the skilled person as suitable for use in the context of the other measurement methodology. That is, I would not consider that any document relating to EIT measurement would provide information which would be useful in the creation of an EEG measurement system. Similarly, I would not consider that any document relating to EEG measurement would provide information which would be useful in the creation of an EIT measurement system.

8. Indeed, EIT and EEG measurement techniques cannot be used together. I will explain why this is the case with reference to Exhibit B to this declaration. Exhibit B shows voltage measurements over a time period of 1 second.

a. For a first period of about 0.3 seconds denoted A, no current injections are made and the voltages which are measured are attributable solely to physiological effects within the brain. It can be seen that the voltages measured have a peak-to-peak amplitude of less than 1mV.

b. For a second time period denoted B current injections are made in accordance with EIT techniques, and the voltage measurements obtained are attributable to the effects of injected current. It can be seen that here the voltage measurements saturate the system, with voltages having peak-to-peak amplitude of more than 10mV being recorded.

c. For a third time period denoted C no current injections are made and the voltage measurements obtained are again attributable solely to physiological effect. It can again be seen that the voltage measurements have a relatively small peak-to-peak amplitude, although the general value of the measurements have been effected by the current injections during the time period denoted B, resulting in generally higher measured voltages in absolute terms.

d. For a fourth time period denoted D current injections are again made and effects as described above with reference to the second time period B can be observed.

9. From Exhibit B it can be seen that as soon as current injections are made, EEG measurements can no longer usefully be made. As such, EEG and EIT measurement are inherently incompatible.

Specific Comments on the Outstanding Rejections

10. The rejected claims require injecting electrical current from an external source between a pair of electrodes at a body surface and collecting the resulting

voltage measurements between pairs of surface electrodes. As those skilled in the art will understand, the claims are therefore directed to "active" processes capable of characterizing structures/events deep within the body under examination.

11. By contrast, electroencephalography (EEG) and electrocardiology (ECG) are entirely "passive" processes which monitor body surface current and/or voltages which naturally occur due to physiological activity within the body.

12. Those having skill in the art recognize that there are fundamental and stark differences between EIT on the one hand, and EEG/ECG on the other hand. Those skilled in the art would clearly not find it "obvious" to transport teachings from one measurement domain to the other.

13. It is not technically feasible to "combine" the EEG Trivedi/John systems with the EIT Boone system. Still further, even if such a "combination" were attempted without regard to technological facts (i.e., *arguendo*), then one still would not arrive at the rejected claims.

14. A person skilled in the art simply would not consider combining features of an EEG system (such as the systems of Trivedi and John) with an EIT system (such as that of Boone). The fundamentally different nature of EIT measurements and EEG measurements is such that techniques used in one measurement methodology cannot be routinely applied to the other. Indeed, in general terms, while many different systems for monitoring brain activity are known, it cannot be the

case that techniques applied in the context of one system would be obvious to apply to any and all other methods.

15. Each of claims 22, 38 and 42 requires that a set of voltage measurements be collected over a predetermined measurement period and that the predetermined measurement period be initiated after a predetermined delay based upon a neurological model following occurrence of a sensory stimulus. This is not the case in any of the cited prior art. Thus, even if all the cited art is somehow (illogically) "combined," one still does not have the claimed invention.

16. Trivedi does not teach monitoring a sensory stimulus response during a predetermined measurement period initiated after a predetermined delay following a sensory stimulus.

17. The Trivedi "Montage Analysis" section is directed to identification of features of interest in data, such as epileptic spikes (25:43-46). An iterative process for identifying a feature of interest such as a peak having a particular shape in the data is described (26:23-26). The "Montage Analysis" section is, therefore, concerned with identifying parts of the data based upon the data itself.

18. Such selection does not imply an inherent time delay after stimulus application. The time delay between application of a stimulus and the time at which a feature occurs in the data cannot reasonably be said to be a delay selected based upon a neurological model. The inherent time delay of Trivedi is based upon the fact that a particular type of peak, such as a peak having a particular shape, happens to

occur at that particular time. To determine the time delay involved, one must also necessarily analyze the data from some earlier time point.

19. On the contrary, applicants' claim 22 explicitly requires that the predetermined delay is based upon a neurological model. That is, the set of voltage measurements is collected after a delay based upon *a priori* knowledge of operation of the nervous system as represented by a neurological model. This is clearly something very different from processing particular data and then later seeking to identify particular patterns in that data – based on characteristics of the data itself. This is what Trivedi does.

20. There is nothing in Trivedi to teach (or suggest) collecting a set of measurements over a predetermined measurement period, the predetermined measurement period being initiated after a predetermined delay (based upon *a priori* knowledge of a neurological model) following occurrence of a sensory stimulus.

21. John does not teach comparing collected measurements with reference measurements. While John teaches that data is analyzed in a computer system to extract numerical descriptors which are compared to a set of norms (paragraph [0011]), it is not true that the comparison of John teaches a comparison to determine normal or abnormal response of the nervous system as recited in applicants' claims 22, 38 and/or 42. None of the cited documents teaches the comparison of collected measurements with reference measurements to determine normal or abnormal response.

22. Furthermore, the collected voltage measurements that are compared with reference measurements as required by applicants' claims 22, 38 and 42 are a set of voltage measurements collected over a predetermined measurement period initiated after a predetermined delay (which is based upon a neurological model) following occurrence of the sensory stimulus. The inventors herein have realized that by comparing voltage measurements that have been carefully collected based upon a neurological model, very specific time-based reactions to sensory stimulus can be analyzed. By carefully selecting the delay based upon a neurological model, specific parts of the nervous system can be checked for normal or abnormal response since particular parts of the brain react at particular times after stimulus application, as is known from an *a priori* model.

23. The measurements of John that are compared with reference measurements are measurements denoting an averaged value indicating a general response of the brain to a stimulus. This can be seen from John at paragraph [0047] which states that brain waves measured at application of a stimulus are measured and averaged to give an "Average Evoked Response." Paragraph [0049] provides an alternative where narrow-band FFT is used to compare power in an EEG when the stimulator is "on" compared with when the stimulator is "off." Indeed, this disclosure of John emphasizes the fundamental difference between (a) processing of measurements obtained at a particular time delay after stimulus application and (b) obtaining an average measurement – which is inherent in EEG-type systems.

24. John, therefore, is concerned with a comparison of a general response to a stimulus of a patient with a reference general response. John is not concerned with comparing (a) a response of a particular part of a nervous system, determined using measurements captured in a predetermined measurement period initiated after a predetermined delay which is based upon a neurological model, with (b) reference measurements as required by applicants' claims 22, 38 and 42.

25. As set out above, a combination of the EEG systems of Trivedi and John with the EIT system of Boone is technologically not feasible. That is, the fundamental difference between the nature of measurements undertaken in an EEG system and the nature of measurements in an EIT system is such that the alleged combination is essentially nonsensical – and not one that a skilled person would make. However, even if such a combination were attempted *arguendo*, a skilled person would nevertheless not arrive at the method of any of applicants' claims 22, 38 and 42.

26. The combination of Trivedi with other cited documents also fails to teach or suggest the claimed invention. Trivedi does not teach the features alleged by the Examiner.

27. Additionally, claim 32 requires that the predetermined delay be selected on the basis of a neurological model and a predetermined part of the nervous system for which a response is to be monitored. In the office action, the predetermined part of the nervous systems is said to be the brain. Notwithstanding

that, for the reasons set out above, none of the cited prior art is concerned with a delay which is selected on the basis of a neurological model – and it should further be noted that none of the cited prior art is concerned with a delay which is based upon a predetermined part of the nervous system for which a response is to be measured. That is, claim 32 is concerned with the situation in which part of the nervous system is selected and, based upon this selection, a delay is determined. Such determination is neither taught nor suggested by any of the cited prior art.

28. The combination of Boone/Trivedi/John now in further view of a fourth reference to Yamazaki '825 also fails to teach or suggest the claimed invention.

29. Fundamental deficiencies of the first three references have already been noted above for parent claim 22 of dependent claims 29-31. Yamazaki does not supply those deficiencies.

30. With respect to independent claim 41, Boone/Trivedi/John also suffers serious deficiencies such as noted above for other independent claims. And, as already noted, Yamazaki does not supply even those deficiencies.

31. Furthermore, Yamazaki only uses a single electrode 21 (Fig. 1) or 47 (Fig. 6) and thus inherently teaches away from applicants' claimed invention.

32. Even if the teachings of Boone and Trivedi are "combined" *arguendo*, one still fails to find any teaching or suggestion of the applicants' claimed invention. For example, note that both independent claims 32 and 37 also require the

predetermined delay to be selected on the basis of a neurological model of the nervous system, etc.

33. Although the cited Polydorides document may teach the additional features, *per se*, of dependent claim 35, Polydorides, this still fails to teach the substance of parent claim 32 – about which Boone is also deficient. Therefore, even if these two references are combined, *arguendo*, there is still no teaching or suggestion of the invention claimed in claim 35. Nowhere in Boone and/or Polydorides is there is a teaching or suggestion of the claim 32/35 requirements, *inter alia*, for a predetermined part of the nervous system to be identified – and then for a predetermined voltage measurement delay to be selected based on a neurological model of the nervous system and that predetermined part of the nervous system for which a response is. That is, even if it is assumed that Polydorides may teach placement of electrodes for maximizing desired measurement sensitivity (in the context of the Polydorides teaching), this still fails to teach or suggest the invention of claim 32/35.

34. For reasons already noted, it is not "obvious" to combine the EEG techniques of Trivedi with the EIT techniques of Boone/Polydorides. Furthermore, as previously noted, applicants are not merely imaging the brain's white matter (Boone and/or Polydorides). Instead, applicants' claim 43 provides an iterative process as a function of different initial time delays so as to derive a time sequence

of images for revealing nervous system responses to a predetermined sensory stimulus in different parts of the subject's brain.

35. The additionally cited Vauhkonen document also does not supply the deficiencies of the other references with which it has been "combined".

36. While, of course, a Kalman filter is known in the prior art, *per se*, applicants have never claimed to have invented a Kalman filter *per se*. Furthermore, merely adding a Kalman filter to the EIT teachings of Boone would not arrive at the applicants' claimed invention. For reasons already noted above, even if all cited references were somehow arguably "combined," one is still left without a teaching or suggestion of the applicants' invention.

37. The lateral geniculate nucleus is located relatively deep within the brain and, therefore, activity of the lateral geniculate nucleus cannot be detected using EEG-type techniques. Thus, it is clear that when considering monitoring of the lateral geniculate nucleus, the skilled person could not possibly consider EEG-type devices as taught by Trivedi and John.

38. I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishably by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 26 day of OCTOBER, 2009.

	Respectfully submitted,	
	By:	
	Christopher John Douglas Pomfrett	

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This constitutes exhibit A to the declaration of Christopher John Douglas Pomfrett made this 26 day of October 2009

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Principles of Neural Science, 4/e

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INTERNATIONAL EDITION

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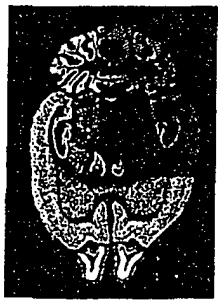


Cover image: The autoradiograph illustrates the widespread localization of mRNA encoding the NMDA-R1 receptor subtype determined by in situ hybridization. Areas of high NMDA receptor expression are shown as light regions in this horizontal section of an adult rat brain.

From Moriyoshi K, Masu M, Ishi T, Shigemoto R, Mizuno N, Nakanishi S. 1991. Molecular cloning and characterization of the rat NMDA receptor. Nature 354:31–37.

Contents in Brief

46

Seizures and Epilepsy

UNTIL RECENTLY, ANALYSIS of brain function relied in large part on observations of the behavioral consequences of brain damage caused by strokes or trauma. These natural "experiments" provided early evidence that distinct brain regions subserve specific functions. Also important in this regard has been the analysis of patients with seizures and epilepsy, because the behavioral consequences of a seizure depend on where in the brain a seizure originates. However in ancient times the dramatic, sometimes bizarre, behavioral manifestations of seizures initially created misperceptions of their neurological origins.

Seizures have fascinated and plagued humanity since antiquity. The Greeks in the time of Hippocrates (circa 400 BC) were aware of the relationship between head injuries and seizure activity involving movements of the opposite side of the body. Despite the observed association with physical injury, epilepsy was widely believed to occur in individuals possessed by evil spirits. Seizures were also associated with prescience or special creative powers. For example, many important historical figures in science, politics, and the arts are thought to have been epileptics. However, in earlier times, epilepsy appears to have been defined according to criteria quite different from those used today; other causes of episodic unconsciousness such as syncope, mass hysteria, or psychogenic seizures were almost certainly called epilepsy. Moreover, historical writings typically described generalized convulsive seizures, and it is thus likely that many cases of partial seizures were misdiagnosed or never diagnosed. Even today, it can be difficult for physicians to distinguish between episodic loss of consciousness and the various types of seizures.

The modern neurobiological analysis of epilepsy began with John Hughlings Jackson's work at Queen Square in London in the 1860s. Jackson realized that seizures need not involve loss of consciousness but could be associated with focal symptoms, such as the jerking of an arm. This observation was the first formal recognition of what we now call partial (or focal) seizures. He also observed patients whose seizures be-

gan with focal neurological symptoms, then progressed to convulsions with loss of consciousness (a so-called Jacksonian march). Another important early development was the first surgical treatment for epilepsy by Victor Horsley, who in 1886 resected cortex adjacent to a depressed skull fracture and cured a patient with focal motor seizures. The modern surgical treatment for epilepsy, however, dates to the work of Wilder Penfield and Herbert Jasper in Montreal in the early 1950s. Medical innovations include the first use of phenobarbital as an anticonvulsant in 1912 by A. Hauptmann, the development of electroencephalography by Hans Berger in 1929, and the discovery of phenytoin (Dilantin) by Houston Merritt and Tracey Putnam in 1937. The physiological features of seizures are not the only consideration in the care and management of patients with epilepsy. Psychosocial factors are also extremely important. In particular, the diagnosis of epilepsy still carries a social stigma that can affect all aspects of everyday life including driving, employment, and educational opportunities.

Classification of Seizures and the Epilepsies Is Important for Pathogenesis and Treatment

Not all seizures are the same. Thus an understanding of the pathophysiology of seizures must first take into account their clinical features. Seizures and the chronic condition of repetitive seizures (epilepsy) are common clinical problems. Based on epidemiological studies in the United States, about 3% of all people living to the age of 80 will be diagnosed with epilepsy. The highest incidence occurs in young children and the elderly. In many respects, seizures represent a prototypic neurological disease in that the symptoms include both "positive" and "negative" sensory or motor manifestations. Examples of positive signs that can occur during a seizure include the perception of flashing lights or the jerking of an arm. Negative signs can include a slowing of normal brain function resulting in depression of consciousness or even transient blindness or paralysis. These symptoms underscore another general feature of seizures: The symptoms are dependent on the location and extent of brain tissue that is affected. Finally, the manifestations of seizures result in part from the involvement of normal tissue with normal excitability.

Seizures can be classified clinically into two categories: partial and generalized (Table 46-1). This simple classification has proved extremely useful to clinicians because the effectiveness of anticonvulsant medications depends on the type of seizure.

Table 46-1 International Classification of Seizures and Epilepsies

Seizures

I. Partial (focal) seizures
   - A. Simple partial seizures (with motor, sensory, autonomic, or psychological symptoms)
   - B. Complex partial seizures
   - C. Complex partial seizures evolving to secondarily generalized seizures

II. Generalized seizures (convulsive or nonconvulsive)
   - A. Absence
     1. Typical (petit mal)
     2. Atypical
   - B. Myoclonic
   - C. Clonic
   - D. Tonic
   - E. Tonic-clonic (grand mal)
   - F. Atonic

III. Unclassified

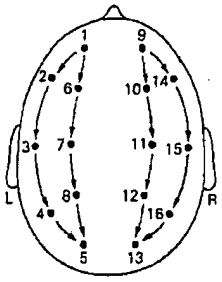
Epilepsies (abbreviated classification)

1. Localization-related epilepsies and syndromes
   - 1.1 Idiopathic with age-related onset (eg, benign childhood epilepsy with centrotemporal spikes)
   - 1.2 Symptomatic (eg, post-traumatic epilepsy)
2. Generalized epilepsies and syndromes
   - 2.1 Idiopathic with age-related onset (eg, juvenile myoclonic epilepsy)
   - 2.2 Idiopathic and/or symptomatic (eg, Lennox-Gastaut syndrome)
   - 2.3 Symptomatic
3. Epilepsies and syndromes undetermined with respect to 1 or 2
   - 3.1 With both partial and generalized seizures (eg, neonatal seizures)
   - 3.2 Without unequivocal generalized or partial features
4. Special syndromes (eg, febrile convulsions)

Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Commission on Classification and Terminology of the International League Against Epilepsy, 1985.

Partial seizures originate in a small group of neurons that constitute a seizure focus. Thus the symptomatology depends on the location of the focus within the brain. Partial seizures can be either *simple partial* (with-

A Standard electrode placement



B EEG of awake human

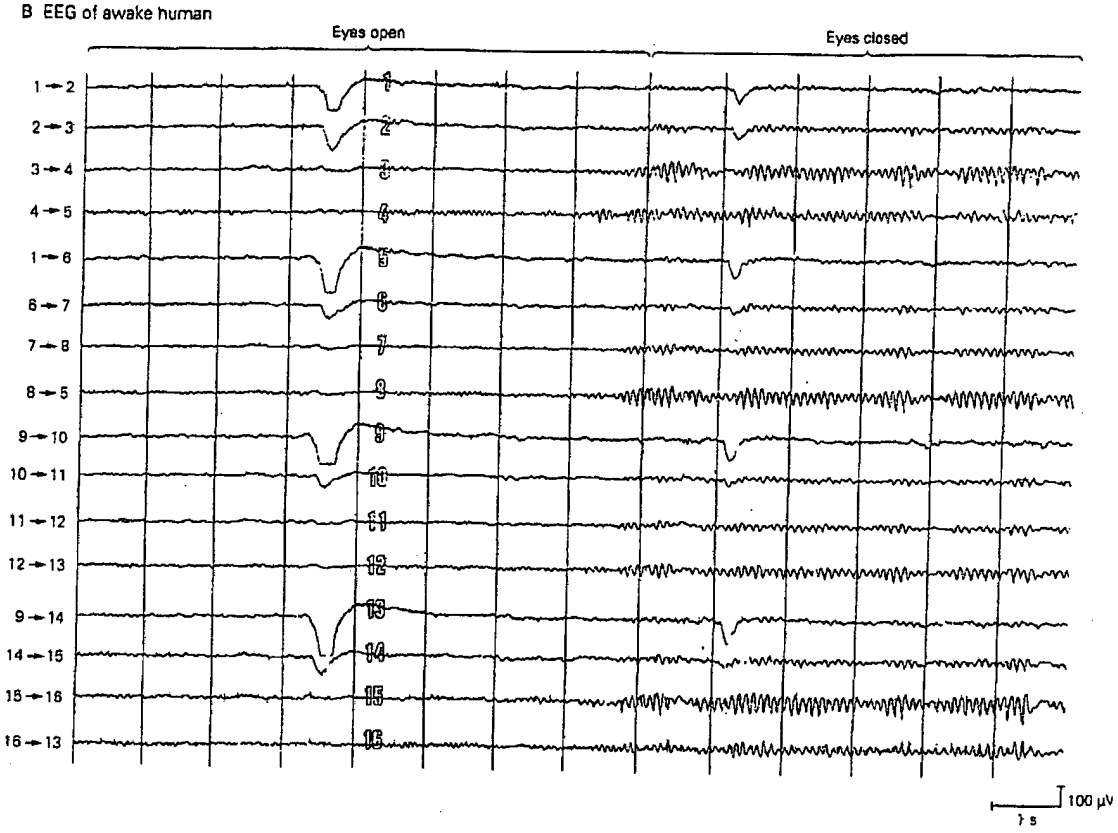


Figure 46-1 The normal electroencephalogram (EEG) in an awake human subject.

A. A standard set of placements for EEG electrodes over the surface of the scalp. The electrical activity between electrode pairs in this bipolar montage is compared.

B. EEG activity of an awake human subject. At the beginning of the recording, the EEG shows low-voltage (circa 20 μV) activity over the surface of the scalp. The vertical lines are placed at 1-s intervals. During the first 8 s the subject rested quietly with eyes open, then closed his eyes. Note the development of larger-amplitude (8–10 Hz) activity over the occipital region (traces 3→4, 4→5, 8→5, 12→13, 15→16, and 16→13). This is the normal alpha rhythm characteristic of the relaxed, wakeful state. Note the slow large-amplitude eye blink artifact at 3.5 s and the artifact on eye closure at 9 s. Calibration 1 s, 100 μV.

out alteration of consciousness) or *complex partial* (with alteration of consciousness). An example of a partial seizure is localized jerking beginning in the right hand and progressing to clonic movements (ie, jerks) of the entire right arm. (Such a seizure formerly was called a focal motor seizure.) If a partial seizure progresses further, the patient may lose consciousness, fall to the ground, rigidly extend all extremities (*tonic phase*), then have jerks in all extremities (*clonic phase*). These symptoms are classified as a secondarily generalized tonic-clonic seizure (formerly called a grand mal seizure).

Symptoms preceding the onset of a partial seizure are called *auras*. Auras commonly include abnormal sensations such as a sense of fear, a rising feeling in the abdomen, or even a specific odor. The aura is due to electrical activity originating from the seizure focus and thus represents the earliest manifestations of a partial seizure. The time after a partial seizure before the patient returns to normal neurological function is called the *postictal period*.

Generalized seizures begin without a preceding aura or focal seizure and involve both hemispheres from the onset. They can be further divided into convulsive or nonconvulsive types, depending on whether the seizure is associated with tonic or clonic movements. The prototypic nonconvulsive generalized seizure is the typical *absence seizure* (formerly called petit mal) found in children. These seizures begin abruptly, usually last less than 10 s, are associated with cessation of all motor activity, and result in loss of consciousness. Unlike a partial seizure, there is no aura or postictal period. Patients may exhibit mild motor manifestations such as eye blinking but do not fall or have tonic-clonic movements. Typical absence seizures have very distinctive electrical characteristics on the electroencephalogram (EEG).

Other generalized seizures can consist only of motor movements (myoclonic, clonic, or tonic) or a sudden loss of motor tone (atonic). However, the most common generalized seizure is the tonic-clonic, or grand mal, seizure. These convulsive seizures also begin abruptly, often with a grunt or cry as tonic contraction of the diaphragm and thorax creates a forced expiration. It is during the tonic phase that the patient may fall to the ground rigid with clenched jaw, lose bladder or bowel control, and become blue *(cyanotic)*. The tonic phase typically lasts 30 s before evolving into clonic jerking of the extremities lasting 1–2 min. This active phase of the generalized tonic-clonic seizure is followed by a postictal phase during which the patient is sleepy and may complain of headache and muscle soreness. Clinically, it can be difficult to distinguish a primary generalized tonic-clonic seizures from a secondarily generalized tonic-clonic seizure with a brief aura. This distinction is not simply academic, as it can be vital to choosing proper treatment as well as pinpointing the underlying cause.

Numerous factors that affect the type and severity of seizures are ignored in the seizure classification shown in Table 46-1. Such factors as the underlying etiology of the seizures, the age of onset, and family history all contribute to the clinical characteristics of the syndrome of recurrent seizures. Recurrent unprovoked seizures constitute the minimal criteria for the diagnosis of *epilepsy*. The factors influencing seizure type and severity can often be recognized in patterns of symptoms resulting in the identification of an *epilepsy syndrome*. Thus a classification of the epilepsies (Table 46-1) continues to evolve, principally based on clinical observation rather than a precise cellular, molecular, or genetic understanding of the underlying pathophysiology. The primary variables are the presence of a focal brain abnormality (localization-related) and whether there is an identifiable cause (symptomatic) or not (idiopathic). The great majority of adult-onset epilepsies are classified as symptomatic, localization-related epilepsy. This category includes such causes as trauma, stroke, tumors, and infections. Understanding the epilepsy syndrome has important implications for prognosis and, for some cases, therapy. Unfortunately many epilepsy syndromes do not fit neatly in this scheme, as indicated by the need for categories 3 and 4 in Table 46-1. One expects that this classification will be greatly refined as the criteria become based on the underlying etiologies rather than clinical observation.

The Electroencephalogram Represents the Collective Behavior of Cortical Neurons

Neurons are excitable cells. Thus it is logical to assume that seizures result either directly or indirectly from a change in the excitability of single neurons or groups of neurons. This view dominated early experimental studies of seizures. Electrical recordings of brain activity can be made with intracellular electrodes that record the electrical activity of individual neurons or with extracellular electrodes that sense action potentials in nearby neurons. Extracellular recording can also detect the synchronized activity of large numbers of cells; such signals are called *field potentials*. At the slow time resolution of extracellular recording (hundreds of milliseconds to seconds), field potentials appear as single electrical transients called *spikes*. These macroscopic events should not be confused with spikes of single neurons, which represent individual action potentials lasting only 1 or 2 ms. The EEG represents a set of field potentials as recorded by multiple electrodes on the surface of the scalp. The set

Box 46-1 The Nature of the EEG

The contribution of single neuron activity to the EEG can be understood by examining a simplified cortical circuit and some basic electrical principles. Pyramidal neurons are the major projection neurons in the cortex. The apical dendrites of pyramidal cells, which are oriented perpendicular to the cell surface, receive a variety of synaptic inputs. Synaptic activity in the pyramidal cells is the principle source of EEG activity.

To understand the contribution of a single neuron to the EEG, consider the flow of current produced by an *excitatory synaptic potential (EPSP)* on the apical dendrite of a cortical pyramidal neuron (Figure 46-2). Current flows into the dendrite at the site of generation of the EPSP, creating a current sink. It then must complete a loop by flowing down the dendrite and back out across the membrane at other sites, creating a current source. The size of the voltage created by the synaptic current is approximately predicted by Ohm's Law ($V = IR$ where V is voltage, I is current, and R is resistance). Because the membrane resistance (R_m) is much larger than that of the salt solution that constitutes the extracellular medium (R_e), the voltage recorded across the membrane with an intracellular

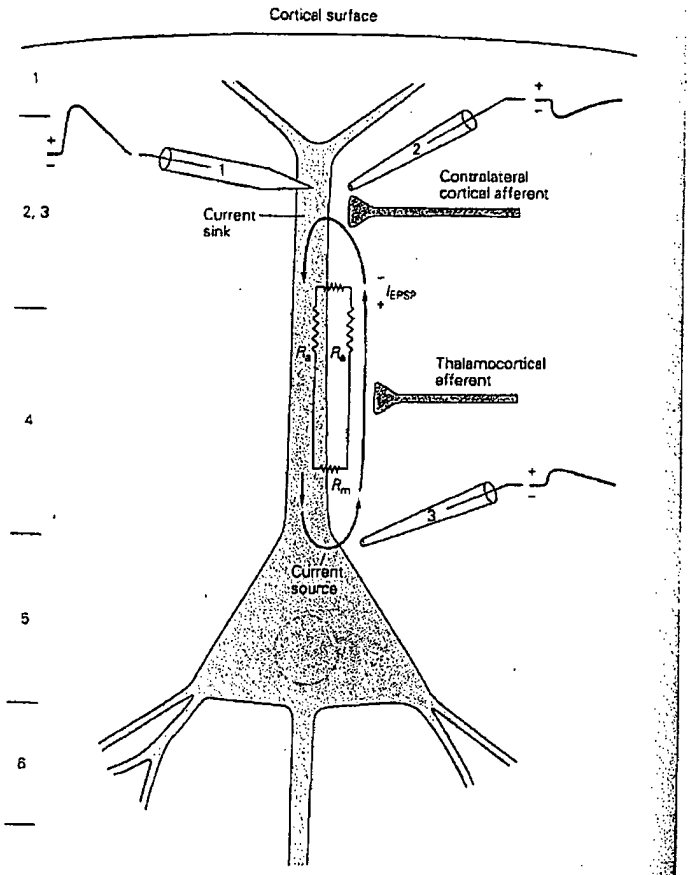


Figure 46-2 The pattern of electrical current flow for an excitatory postsynaptic potential (EPSP) on the apical dendrite of a pyramidal neuron in the cerebral cortex. The activity is detected by an intracellular electrode (1), an extracellular electrode positioned near the site of the EPSP in layer 2 of the cortex (2), and an extracellular electrode near the cell body in layer 5 (3). At the site of the EPSP (sink), current flows across the cell membrane into the cytoplasm. The current (I_{EPSP}) then flows down the dendritic cytoplasm and completes the loop by exiting through the membrane (source). Note that the polarity of the potentials recorded by extracellular electrodes at the sink and the source are opposite. The intracellular electrode has the same polarity regardless of the site of the input. R_m, R_e, and R_e are the resistances of the membrane, cytoplasm, and extracellular space, respectively.

electrode (electrode 1) is also larger than at an extracellular electrode positioned near the current sink (electrode 2).

At the site of generation of an EPSP the extracellular electrode detects current flowing away from the electrode into the cytoplasm as a downward deflection. However, an extracellular electrode near the source has an opposite polarity (compare electrodes 2 and 3, Figure 46-2). The situation is reversed if the site of the EPSP generation is on a proximal dendrite. In the cortex excitatory inputs from the contralateral hemisphere contact the pyramidal neurons primarily on distal parts of the dendrite in layers 2 and 3, whereas thalamocortical inputs terminate in layer 4. The activity measured at a surface EEG electrode will have opposite polarities for these two inputs, even though the basic electrical event, membrane depolarization, is the same. EPSPs in superficial layers and *inhibitory postsynaptic potentials (IPSPs)* in deeper layers appear as upward (negative) potentials, whereas EPSPs in deeper layers and IPSPs in superficial layers have downward (positive) potentials (Figure 46-3). Thus cortical synaptic events cannot be unambiguously determined from EEG recordings alone.

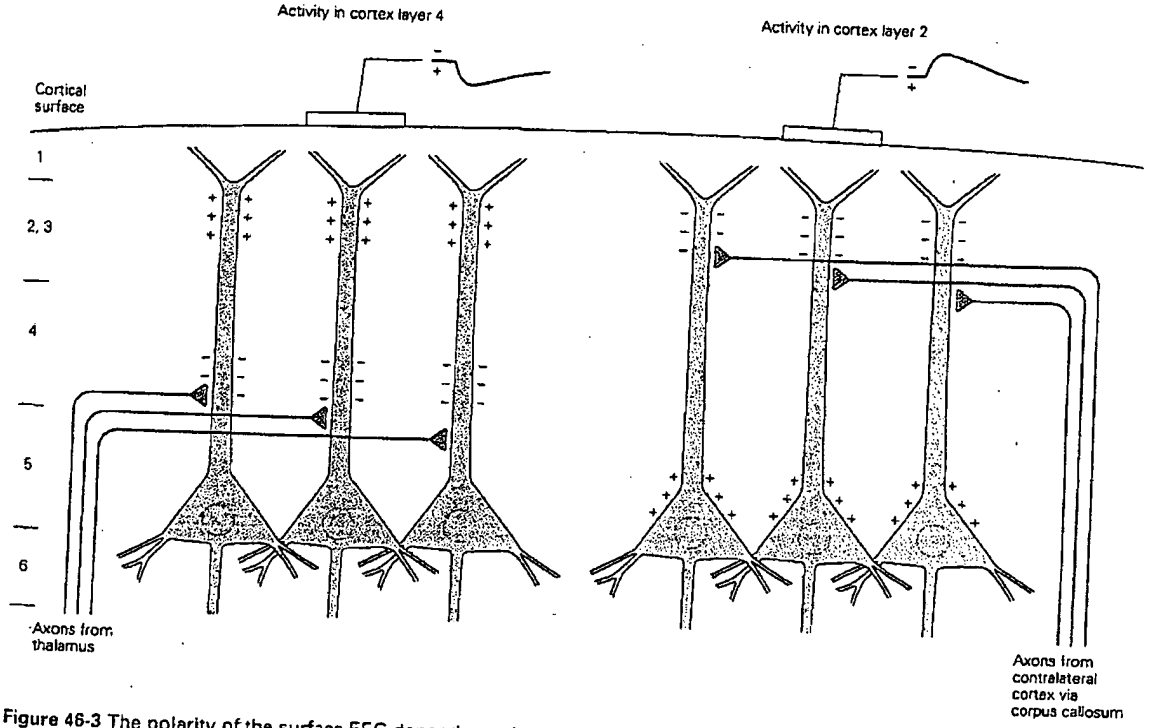


Figure 46-3 The polarity of the surface EEG depends on the location of the synaptic activity within the cortex. A thalamocortical excitatory input in layer 4 (left) causes a downward deflection at the surface EEG electrode because the EEG electrode is nearer to the source. In contrast, excitatory input from the contralateral hemisphere in layer 2 (right) causes an upward deflection because it is nearer to the sink.

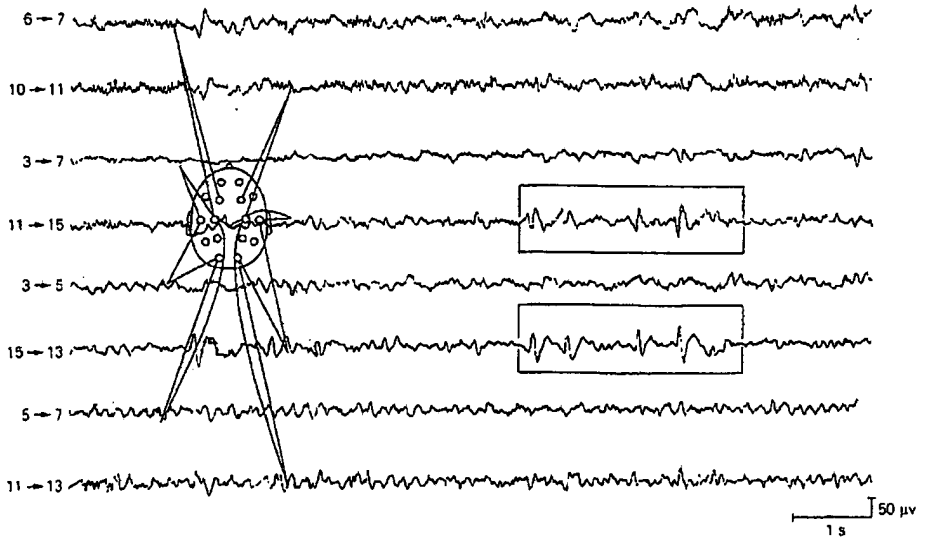


Figure 46-4 Electroencephalogram (EEG) activity in a patient with epilepsy shows focal sharp waves in the EEG electrodes located over the right temporal area (enclosed in boxes). Note that this paroxysmal activity arises suddenly and disrupts the normal background EEG pattern. The focal abnormality suggests that the seizure focus in this patient is in the right temporal lobe. Because the patient had no clinical seizures during the recording, these are interictal spikes. (Adapted from Lothman and Collins 1990.)

of locations for electrodes placed on the skull is called a *montage*. Montages may consist of monopolar arrangements in which each electrode records the electrical activity at a site *(active electrode)* relative to a distant site *(indifferent electrode)*, such as the ear lobe. Alternatively, pairs of scalp electrodes can be interconnected and in this case both electrodes are active. A typical bipolar montage is shown in Figure 46-1A.

The electrical activity of the EEG is an attenuated measure of the extracellular current flow from the summated activity of many neurons. However, not all cells contribute equally to the EEG. The surface EEG predominantly reflects the activity of cortical neurons close to the EEG electrode. Thus deep structures such as the hippocampus, thalamus, or brain stem do not contribute directly to the surface EEG. The contributions of individual nerve cells to the EEG as recorded at the cortical surface are schematized in Box 46-1.

Because the electrical activity originates in neurons in the underlying brain tissue, the waveform recorded by the surface electrode depends on the orientation and distance of the electrical source with respect to the electrode. The EEG signal is inevitably distorted by the filtering and attenuation produced by intervening layers of tissue and bone, which act like resistors and capacitors in an electric circuit. Thus the amplitude of EEG potentials (microvolts) is much smaller than the voltage changes in a single neuron (millivolts).

The surface EEG shows typical patterns of activity that can be correlated with various stages of sleep and wakefulness, and with some pathophysiological processes such as seizures. EEG patterns are characterized by the frequency and amplitude of the electrical activity. The normal human EEG shows activity over the range of 1–30 Hz with amplitudes in the range of 20–100 μV. The observed frequencies have been divided into several groups: alpha (8–13 Hz), beta (13–30 Hz), delta (0.5–4 Hz), and theta (4–7 Hz). Alpha waves of moderate amplitude are typical of relaxed wakefulness and are most prominent over parietal and occipital sites. Lower-amplitude beta activity is more prominent in frontal areas and over other regions during intense mental activity. Alerting a relaxed subject results in so-called desynchronization of the EEG, with a reduction in alpha activity and an increase in beta (Figure 46-1B). Theta and delta waves are normal during drowsiness and early slow-wave sleep, but if present during wakefulness represent a sign of brain dysfunction.

As neuronal aggregates become synchronized, the summated currents become larger and can be seen as

abrupt changes from the baseline activity. Such "paroxysmal" activity can be normal, eg, the 1–2 s, 7–15 Hz episodes of high-amplitude activity that represent sleep spindles. However, a sharp wave or EEG spike can also represent a clue to the location of a seizure focus in a patient with epilepsy. An example of localized high-amplitude sharp waves is shown in Figure 46-4.

Partial Seizures Originate Within a Small Group of Neurons Known as a Seizure Focus

Despite the range of seizure types that can be distinguished by their clinical features, the generation of seizure activity can be understood by considering two characteristic electrographic patterns: the partial seizure and the (primary) generalized seizure. These two seizure types have different pathophysiological substrates.

The defining feature of partial (and secondarily generalized) seizures is that the abnormal electrical activity originates from a seizure focus. The *seizure focus* is a small collection of neurons that trigger enhanced (epileptiform) excitability. Enhanced excitability may result from many different factors such as altered cellular properties or altered synaptic connections caused by a local scar, blood clot, or tumor. A discrete focus in the primary motor cortex may cause twitching of a finger or jerking of a limb (simple partial seizure), whereas a focus in the limbic system is often associated with unusual behaviors or an alteration of consciousness (complex partial seizure). The phases in the development of a partial seizure can be arbitrarily divided into the interictal period, followed by neuronal synchronization, seizure spread, and finally secondary generalization. Different factors contribute to each of these phases. Most of our knowledge about the pathophysiology of seizures is derived from studies of animal models of partial seizures. In these studies, a seizure is induced by acute injection of a convulsant agent or by focal electrical stimulation. This approach has provided a good understanding of electrical events within the focus during a seizure as well as during the interictal period (Figure 46-5). The development of in vitro tissue slice preparations has also been particularly valuable in the study of seizures (Box 46-2).

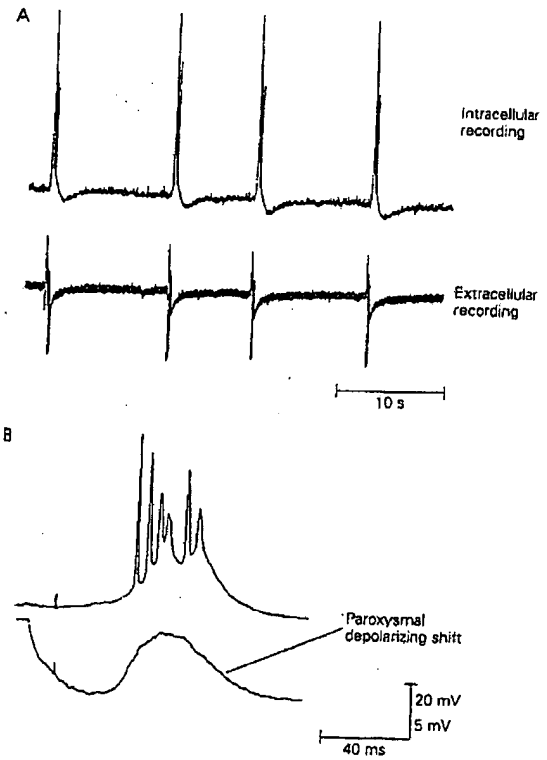


Figure 46-5 Interictal spikes correspond to synchronized discharges of a group of neurons in an in vitro brain slice. (Adapted from Wong et al. 1984.)

A. Rhythmic discharges are present in the intracellular recording from a normal hippocampal pyramidal cell (top trace). The discharge of many neurons is manifest as a synchronous interictal spike as recorded by an extracellular electrode (bottom trace).

B. The brain slice is perfused with bicuculline, which blocks inhibition mediated by γ-aminobutyric acid $(GABA)_A$ receptors. A hippocampal pyramidal cell is depolarized and fires several superimposed action potentials (top trace). Injection of current to hyperpolarize the membrane and prevent action potential firing reveals the large paroxysmal depolarizing shift characteristic of neurons in a seizure focus (bottom trace).

Neurons in a Seizure Focus Have Characteristic Activity

Experimental studies of partial seizures have long been directed at how electrical activity in a single neuron or group of neurons leads to the generation of a seizure. Each neuron within a seizure focus has a stereotypic and synchronized electrical response called *the paroxysmal depolarizing shift* (PDS). The PDS consists of a sudden, large (20–40 mV), long-lasting (50–200 ms) depolarization (see Figure 46-5B), which triggers a train of action potentials at the peak of the PDS. The PDS is followed by an afterhyperpolarization. The PDS and the afterhyperpolariza-

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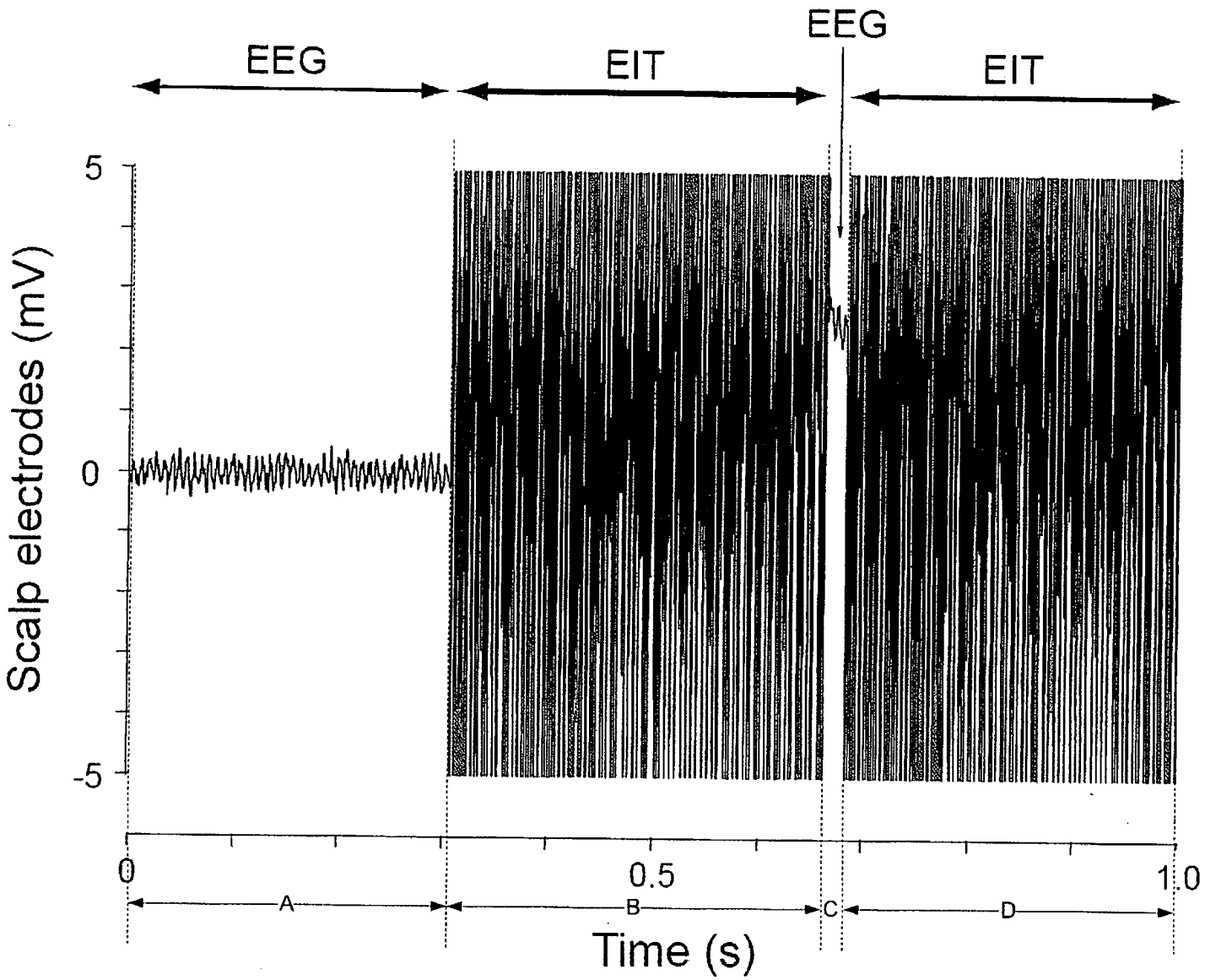
This constitutes exhibit B to the declaration of Christopher John Douglas Pomfrett made this 26 day of October 2009


EEG
EIT
EEG
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5
0
-5
Scalp electrodes (mV)
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